ON RETINE

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Many years ago, working with Jane McLaughlin, I found that certain tissue extracts inhibit malignant growth. We called the inhibitive substance "retine" and tried to isolate it in collaboration with Dr. L. Együd. We found that purified tissue extracts showed, in their infrared, a ketone and aldehyde absorption. This suggested that the inhibiting substance may be a ketone aldehyde, a glyoxal derivative. This assumption seemed attractive because it was known that all tissues contain a very active enzymic system, glyoxalase, capable of transforming ketone aldehydes into the corresponding oxyacids. In the first half of this century, this glyoxalase occupied many of the leading biochemists, who were trying to find its substrate, a glyoxal derivative, with no success.

In order to approach this problem, we, along with Dr. L. Együd, synthetized a number of methylglyoxal derivatives, the whole series up to C^{14}. We found that the lower members inhibited proliferation of *E. coli* in very low concentrations. The maximum activity was reached with six carbon atoms and then declined again with lengthening of the chain. The incorporation of labeled amino acids and nucleotides showed that the inhibition of growth was due to an inhibition of protein synthesis on the ribosome level. We also found that cysteine or other sulfhydryl derivatives readily abolished this inhibition.

The cardinal question, thus, was: do tissues contain glyoxal derivatives? Methylglyoxal derivatives are easy to discover since ketone aldehydes give a red osazone with dinitrophenylhydrazine. Tissue extracts do not do so. Thus, either there were no ketone aldehydes, or else their CO groups were masked, possibly by SH. In order to eliminate the SH we treated the tissue extracts with arsenious oxide and found that after this treatment the extracts gave a very rich crystalline precipitate of a deep red osazone. In collaboration with Professor Fodor and J. P. Sachetto of the Laval University of Quebec, the constitution of this substance was studied and it was found to be the osazone of glucosulose, a 2-keto-3-deoxyglucose which can easily be formed from glucose by a dismutation between carbons 2 and 3. On chromatography we found that our tissue extracts contained three additional glyoxal derivatives which I will simply denote as A, B, and C.

The glucosulose was synthetized by Fodor and Sachetto. It is biologically inactive. Thus, contrary to our expectations, it is not identical with "retine." It appeared in our extracts only after treatment with As_2O_3.

Substance A also gives a red osazone, and is thus a glyoxal derivative or its isomer. It is present in our extracts in relatively great quantity prior to arsenic treatment, and can thus be no artifact. It forms an osazone only if present in high purity. It inhibits protein synthesis in trace amounts, and may thus be identical with "retine."

Substances B and C are biologically inactive, are present in relatively smaller

concentration, and give osazone only after treatment with arsenic. We are at present engaged in the isolation and identification of A.

To sum up, our experiments indicate that ketone aldehydes are normal constitutents of tissues, and can have a high biological activity. The chemical signal which regulates cell division may thus be a ketone aldehyde. These glyoxal derivatives, together with the enzymes responsible for their formation and deletion, form a complex system with complex equilibria, the disturbance of which may be connected with cancer.